Frequency and associated Risk Factors of Diabetic Foot Infection: A review on the Management and Prevention.

By

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A thesis submitted to the Department of Mathematics and Natural Sciences in partial fulfillment of the requirements for the degree of Bachelor of Science in Biotechnology.

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Declaration

It is hereby declared that,

1. The thesis submitted is my/our own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

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Approval

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Abstract

Diabetic foot infection (DFI) is a soft tissue or bone infection below the malleoli, leads to lower extremity amputation in 85% of diabetics which results in high-cost hospitalization and a higher mortality risk. Almost 6.3% of people worldwide have diabetic foot infection, patients with type 2 diabetes being the most affected. Peripheral arterial disease (PAD) and diabetic neuropathy are the two main risk factors of diabetic foot but poor sugar control, chronic ulcer, previous lower extremity amputation and lifestyle etc. also play contributing role. Management of DFI starts with proper assessment and that is the key to design an appropriate treatment strategy based on extent and severity of the infection including comorbid conditions. Proper treatment reduces the risk of amputation and infection at the same time improves quality of life as well as health care costs. Though antibiotic therapy and surgical debridement are the most effective way of treating infections but now-a-days several emerging treatments have developed. Diabetic foot infection is preventable. Practicing a healthy lifestyle is must to prevent and control diabetic related foot diseases. This review aims to summarize major risk factors associated with frequent onset of diabetic foot ulcers with a special emphasis on management and prevention.

Dedication

I dedicate this thesis to my parents and my grandmother.

Acknowledgement

I express my deepest gratitude to the almighty to have enabled and aided me in successfully completing my thesis. Throughout my venture I have worked with many people and I express my deepest gratitude and warmest thanks to all of them.

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Chapter 1 Introduction

1.1 What is Diabetes ?

Diabetes mellitus (DM), commonly referred to as diabetes, is a disorder of carbohydrate metabolism characterized by a high blood sugar level over a longer period. It was first identified as a disease associated with 'sweet urine' (high levels of blood glucose leads to spoilage of glucose in urine) and excessive muscle loss. Glucose is the primary source of energy of our body cells that make up muscles and tissues. It's also the main source of fuel of our brain. Usually insulin, a hormone that is released by the beta cells of pancreas, tightly control the blood glucose level. In case of diabetic patient, the beta cells may become dysfunctional, resulting in insufficient production of insulin or their muscle and adipose cells may be resistant to the effects of insulin, in both cases cause hyperglycemia (high blood sugar). The global diabetes prevalence in 2019 is estimated to be 9.3% (463 million people), the prevalence is higher in urban (10.8%) than rural areas (7.2%) (Saeedi et al., 2019).

1.2. Types of Diabetes

Diabetes occurs in different forms. Among them mostly three types are common – Type 1 diabetes, Type 2 diabetes, and gestational diabetes. In Type 1 diabetes (formerly referred to as insulin-dependent diabetes mellitus, IDDM or juvenile-onset diabetes), body's immune system destroys the cells in pancreas as a result body cannot produce insulin. Most common in children and young adults and patients must need insulin to stay alive. According to WHO, there were 9 million type 1 diabetic patients in 2017. Neither its cause nor the means to prevent it are known. Type 2 diabetes (formerly called non-insulin-dependent diabetes mellitus, NIDDM or adult-onset diabetes) is the result of body's ineffective use of insulin. It is the most common type of diabetes (more than 95% of people with diabetes have type 2 diabetes) usually occurs after age 40 and becomes more common with increasing age. But recently it's also occurring increasingly frequently in children. This type of diabetes is strongly associated with obesity and physical inactivity. Lastly gestational diabetes which develops in some woman during their pregnancy and most of the time recovers after the child's birth. This gestational diabetes can lead to type 2 diabetes later in life.

1.3. Signs and symptoms of Diabetes

The common signs and symptoms of diabetes are frequent fatigue, increased hunger, increased thirst, unexplained weight loss, repeated infections, dry mouth, frequent urination, burning, pain itching, decreased vision, presence of dark patches on various body parts, i.e., arm pit, neck, groin etc., delayed wound healing (Ramachandran, 2014). Most of the time, diabetes is diagnosed in the later stage when medicine is required. Half of the population suffering from diabetes are not aware of their disease in the early stage (Jahani & Mahdavi, 2016). Though early detection and treatment of diabetes is an important step toward keeping people with diabetes healthy.

Diabetes is a lifelong disease, so if it is left untreated, can cause many complications. Long term complications of diabetes develop gradually. Serious long-term complications include

cardiovascular disease, nerve damage (neuropathy), chronic kidney damage (nephropathy), damage to the eyes (retinopathy), foot damage, hearing impairment, Alzheimer's disease etc. Among all the complications, diabetic foot ulcer (DFU) or diabetic foot infection (DFI) is the most prevalent one.

1.4. What is DFI (Diabetic foot infection)?

Diabetic foot infection (DFI) is the infection of soft tissue or bone below the malleoli (A bony projection with a shape likened to a hammer head, especially each of those on either side of the ankle). Nearly 460 million people have diabetes worldwide and it is estimated that as many as 148 million of those people develop foot ulcer (DFU) in their lifetime (Chastain et al., 2019). Diabetic patients have at least a 10-fold greater risk of being hospitalized for soft tissue and bone infections of the foot and 30-fold higher lifetime risk of undergoing a lower-extremity amputation compare to those without diabetes (Lavery et al., 2006). Among the total 6.3% of global diabetic foot ulcer prevalence, North America has the highest (13.0%). Asia, Europe, and Africa have 5.5%, 5.1% and 7.2% respectively (Zhang et al., 2017). According to research, the prevalence of diabetes in Bangladesh is around 6% which is also an alarming rate ("Standards of Medical Care in Diabetes - 2007," 2007). Also, by visiting 16 Bangladeshi hospitals and medical centers, a study showed that 44.5% of the study population was at risk of DFI (Banik et al., 2020). Diabetic foot disease approaches almost 50% of mortality rate worldwide (estimated 5-year mortality) and it is higher than that for prostate cancer, breast cancer, and Hodgkin lymphoma (Chastain et al., 2019).

1.5. Risk Factors of DFI

The most common risk factors for DFI are peripheral vascular disease and diabetic neuropathy. Diabetes cause nerve damage which ultimately leads to neuropathy. Damaged nerves in legs and feet do not let the patient to feel any pain, sore, heat or cold there. As a result, untreated cut or infection gets worse. Besides, peripheral vascular disease is a blood circulation disorder. Arteries or veins become narrow or block. Therefore, blood flow is disrupted and can cause pain and infection in the legs. Several other risk factors include poor glycemic control, chronic ulceration (duration more than 30 days), previous lower extremity amputation, traumatic foot wound, improper footwear & lifestyle (Lavery et al., 2006). Studies showed that 15% of diabetes patients develop a foot ulcer during their lifetime. Proper assessment, antibiotic therapy, surgical debridement, dressings to facilitate a moist wound environment and exudate control, wound off-loading, vascular assessment, infection, and glycemic control are all standard and common practices in DFU management.

Long-term care is required in many circumstances. The cost of treatment is substantial. According to one study, the cost of amputation was 5.54 times greater than the cost of standard treatment. New strategies for treating DFI are being researched to make them more successful and less expensive.

1.6. Objective

The objectives of this study are to estimate the frequency of occurrence of diabetic foot infection in diabetic patients, to discuss the major risk factors and available management facilities and finally to assess the preventive measures.

Chapter 2: Frequency of Diabetic Foot Infection

A diabetic foot infection, most simply defined as any inframalleolar infection in a person with diabetes mellitus. It can appear as the result of a small injury and can develop into serious wounds over time. IDSA classifies the infection into 3 categories (mild, moderate, and severe) which is based on local and systemic manifestations, and extent of infection (Sciences, 2019).

Day by day prevalence of DFI is becoming alarming. It was shown to be present in 6.3 percent of people worldwide, with type 2 diabetes being the most affected (Zhang et al., 2017). In 1990, the global prevalence was 211.2 million; by 2017, it has risen to 476 million. The disease frequency varies depending on county, age, sex, lifestyle etc. For example, in North America the prevalence is highest (13.0%). Asia, Europe, and Africa have 5.5%, 5.1% and 7.2% respectively (Lin et al., 2020).

Like in some other developing countries, the ratio in Bangladesh is also high. According to International Diabetes Federation there were 8.4 million adults living with diabetes in 2019, and it will be double by 2045. As the prevalence of diabetes increases, the diabetes related complications are also increasing. Here the prevalence of DFU is around 6% ("Standards of Medical Care in Diabetes - 2007," 2007). Delay identification, poor management of cases, lack of effective treatment techniques, treatment cost etc are the contributing factors for the high percentage in this country.

According to Yazdanpanah et al., about 15–25% of patients with diabetes may develop foot ulcer throughout their lifetime. The annual rate of developing diabetic foot ulcer in patients is around 2%, but it may increase 17–60% if there is any past history of foot ulcer (Yazdanpanah et al., 2018). Diabetic foot ulcer is one of the most common cause of hospitalization in diabetic patients. Every 30 seconds in the world, a lower limb is amputated due to diabetes (Yazdanpanah et al., 2018). After the first ulcer or gangrene within a year, the likelihood of amputation is 34.1% (Chun et al., 2019). In addition, the estimated mortality rate is 5.5% (Chun et al., 2019). High amputation rate increases the mortality. Diabetes and its associated pathological conditions also have socioeconomic impact. As the treatment cost is high, so in poorer countries, most of the people don't go for treatment. Diabetic foot ulcer needs a long-time treatment and about 20% to 33% of costs related to diabetes mellitus are involved with treatment (Chun et al., 2019).

Chapter 3: Risk Factors Associated with Diabetic Foot Ulcer (DFU)

3.1. Presence of Peripheral Arterial Disease

Peripheral arterial disease (PAD) refers to partial or complete obstruction of the peripheral arteries, typically the arteries in the legs. The most common symptom of PAD is intermittent claudication, which is calf and lower extremity pain that develops with walking or other exertion. PAD is more common among people with diabetes due to the higher risk of arterial atherosclerosis (formation of plaque in the walls of arteries resulting block in blood flow) associated with this metabolic disorder (Boyko et al., 2015).

Diabetes damages blood vessels by inflammation and atherosclerosis. Narrow arteries result into ischemia, (the circulation of blood in the arteries is restricted and the availability of oxygen, glucose, and critical nutrients to tissues in the body is substantially reduced). When poor circulation affects the arteries of the feet and hands, it develops peripheral artery disease (PAD). PAD restricts the supply of oxygenated and nutrient-rich blood, so it increases the risk of ulcer. If an ulcer occurs, PAD will make the ulcer heal slowly or not at all. A diabetes patient has an approximately 25% risk of developing ulcerations (Cardoso et al., 2019). According to studies, one out of every three adults over 50 with diabetes is likely to have PAD. Identification of PAD in patients with foot ulceration is very critical because they mostly lack typical symptoms, such as intermittent claudication (rest pain), even in the presence of severe tissue loss (Boyko et al., 2015). The American Diabetes Association (ADA) recommends the ankle-brachial index (ABI) as a measure of detection for all diabetic individuals over 50 years of age or those who have suffered from the disease for more than ten years. (Ayala et al., 2017)

3.2. Diabetic Neuropathy

Neuropathy is the damage or dysfunction of nerves that typically results in numbness, tingling, muscle weakness and pain in the affected area. Diabetic Neuropathy refers to the damage in the nervous system caused by diabetes (high levels of lipids or sugar in the blood) (Richards et al., 2018). Diabetic peripheral neuropathy is the most common form of neuropathy around the whole world and the prevalence is higher among people with type 2 diabetes (Richards et al., 2018). According to the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), one-third and a half people with diabetes have neuropathy. According to Volmer-Thole & Lobmann, 2016, approximately 50% of diabetes patients develop symptomatic peripheral neuropathy within 25 years of disease onset. On the contrary, diabetic neuropathy is a factor in almost 90% of diabetic foot ulcers because in addition to the sensory, motor, and autonomic nerves, diabetic neuropathy also damages the immune system and impairs the body's ability to fight infection (Boyko et al., 2015). When a diabetic patient's sensory nerves are injured, he or she loses the ability to feel pain, heat, and cold in their feet. As a result, there will be no preventive response to potential causes of foot injuries. Damage to motor nerves can also cause muscle wasting-resulting in a motor imbalance of extensor muscles, which may develop foot deformities. Deformed foot structure makes it difficult to wear regular shoes and causes blisters and ulcers in the foot. Because of sensory neuropathy, that area of the foot remains numb, and if

not treated promptly, the ulcer may become intense and spread to the bone, resulting in a serious complication that may necessitate surgery.

3.3. Poor glycemic control

Poor glycemic control means persistently raised blood glucose and glycosylated hemoglobin levels. High blood glucose level weaken a person's immune system defenses and it allows bacteria to grow and allow infections to develop more rapidly. According to a review, various types of infections notably skin, mucous membrane, soft tissue, urinary tract, respiratory tract, and surgical and hospital-associated infections are caused by diabetes (Akash et al., 2020). As uncontrolled hyperglycemia damages overall immunity of the diabetic patient, they become immunocompromised so any kind of infection which easily leads to serious conditions (Akash et al., 2020). High sugar level slows down the healing process, therefore, patients with diabetes have higher risk of infections and being wound. Researchers found that the risk of diabetic foot infection increases 1.4-fold among patients with HbA1c greater than 7.5% (58 mmol/mol) (Zacay et al., 2021).

3.4. Chronic Ulceration

Chronic ulcers are described as spontaneous or traumatic lesions in the lower extremities that do not respond to initial therapy and eventually persist despite adequate care and do not heal in a distinct period of time with an underlying etiology related to systematic disorder (Suthar et al., 2017). In diabetic patients the risk of developing a chronic ulcer is very high because of immunocompromised body. 15–25% of patients with diabetes develop foot ulcer during their lifetime.(Yazdanpanah et al., 2018). Chronic nonhealing foot ulcers occur in approximately 15% of patients with diabetes.(Andrews et al., 2015). High blood glucose level slows down the healing process as well. If chronic ulcer occurs, it can then lead to serious infection which may require amputation or increase the risk of serious health problem.

3.5. Prior lower extremity amputation

Lower-limb amputation is the elimination of a part or multiple parts of the lower limb. Diabetes mellitus, peripheral vascular disease, neuropathy, ulcer, and trauma are the main leading cause for amputation. Diabetic patients are immunocompromised and associated risk factors such as neuropathy and peripheral vascular disease, so they are more prone to develop foot ulcers, which can lead to amputation. Patients with prior (LEA) have a higher risk of re-ulceration than those who only have DFU (Rathnayake et al., 2020). One study (4 years of follow-up) mentioned that 40% of patients with previous LEA relapsed within 1 year, compared to 30% in the group without LEA (APELQVIST et al., 1993). In case of re-amputation, LEA is an important and independent risk factor (Rathnayake et al., 2020). A study of 277 patients showed re-amputation rates at 1, 3 and 5 years were 26.7%, 48.3% and 60.7% respectively (Izumi et al., 2006). The

mortality rate among diabetic patients with LEA is also higher compare to without LEA (Hoffstad et al., 2015).

3.6. Traumatic Foot Wound

Traumatic wounds or extensive wounds are commonly defined as cuts, lacerations, or puncture wounds that cause damage to both the skin and underlying tissues. As foot has its role in weight bearing so it can be easily exposed to direct trauma and a traumatic foot wound can lead to a foot ulcer. Other vital independent risk factors for foot infection include wounds that penetrated to the bone, recurrent wounds, long-term wounds (wounds that are more than 30 days old), peripheral vascular disease, and neuropathy (Lavery et al., 2006). According to a study, previous trauma is a significant contributing factor of diabetic foot ulcer (Banik et al., 2020).

3.7. Age

Age is an important triggering factor for complications-increasing the likelihood of developing any kind of disease. Diabetes has a prevalence of 19.9 percent among people aged 65 to 74 years (Navarro-Peternella et al., 2016). All diabetic foot complications increase significantly with age. (Al-Rubeaan et al., 2015). According to Lavery (2008), diabetic patients over 65 years of age have the higher risk of foot ulcer. The increased sepsis and reduced angiogenesis (the development of new blood vessels) in elderly diabetics also make them more prone to foot ulcers. Moreover, persons in their old age, have a physiological impairment to recovery. A study showed that the amputation rate of limb is 3.6 percent in patients aged 65 or older. (Al-Rubeaan et al., 2015)

3.8 Sex

Gender and biological sex are risk factors for a variety of diseases, including metabolic disorders like diabetes. According to CDC (Center for Disease Prevention and Control), men are more likely to get type 2 diabetes than women. Also, diabetic related foot disease is more frequent in males than it is in women. Study showed that male patients have a higher risk of developing a foot ulcer (Khalique, 2014). The probable cause may be due to having lower joint mobility and greater foot pressures than female patients. Men’s higher average height and the prevalence of peripheral insensate neuropathy can also be contributing factors. The risk of amputation also differs between two sexes. Though the difference is very minor. Lei Fan and Xue-Jian Wu in their systematic review stated that male diabetic patients are associated with an increased risk of amputation than female diabetic patients (Fan & Wu, 2021). Hospital discharge report in the United States also indicated that males had 1.4-2.7 times higher risk of amputation than of females (Khalique, 2014).

3.9. Improper footwear

Improperly fitted shoes also play an important role in causing foot injuries. Shoes that are too small most commonly generate constant local pressure on the inner and outer surfaces of the foot. Too big shoes can cause friction ulcers on the back of the heel because the foot slips in the shoe. A study reported that skin rubbing from footwear was the most common cause of ulceration. In that study an estimated 20.6% of foot ulcers in patients with diabetes were due to the shearing force applied to the skin from ill-fitting shoes (Jayasinghe et al., 2007). In rural areas of developing countries walking barefoot and using poor footwear is very common. That ultimately causes injury by sharp or hard objects and develop infection (Jayasinghe et al., 2007). Another study among 174 diabetic patients showed that more than 71.3% of diabetics wore poor grade footwear (Jayasinghe et al., 2007). In Asian subcontinent, the hot climate forces a substantial number of people to wear open footwear which is classified as poor grade. This kind of footwear doesn't give any protection to the feet.

3.10. Lifestyle

Lifestyle has a significant impact in the development of diabetic foot ulcers. Obesity, smoking, physical inactivity, and poor foot care, all contribute to the development of diabetic foot ulcers (Jalilian et al., 2020). It has been confirmed that cigarette smoking is an independent risk factor for diabetic neuropathy (Xia et al., 2019). Cigarette smoke is a source of free radicals and oxidants. Therefore, potential to cause cellular oxidative stress in a variety of organs, including the nervous system and blood vessels, leading to cellular damage and even cell death or apoptosis. Smoking is linked to insulin resistance and chronic cigarette smokers are insulin resistant and hyper insulinemic (Xia et al., 2019).

Obese people with diabetes have higher risk of developing peripheral neuropathy, peripheral arterial disease, and incapable/impotent to self-care. Overweight diabetic individuals more likely to develop diabetic foot ulcers 2.1 times higher than the normal-weight diabetic patients (Mariam et al., 2017). In case of obese people, higher foot pressure and overweight may substantially decrease the normal blood circulation pattern in the lower extremities and may develop diabetic foot ulcers.

Self-care can be another important factor for developing DFU. Sedentary behavior (certain activities in a reclining, seated, or lying position requiring very low energy expenditure), physical activity level, etc. significantly increase the risk for type 2 diabetes and cardiovascular complications. Orlando et al. showed in his study that sedentary time (SED-time) is an independent and powerful predictor of DFUs in people with diabetic peripheral neuropathy and prolonged sedimentary time increases the risk of ulcer development up to three times (Orlando et al., 2021).

In addition, diabetic patients already have poor immune system which makes them more susceptible to infection. If patient have excessive blood sugar level, it can damage their nerve

cells in the feet. As a result, people may lose their sense of feeling in their feet. That's why patients need to provide special attention to their feet.

Chapter 4: Management of Diabetic Foot Ulcer (DFU)

4.1. Proper Assessment

Proper assessment means the ability to define the ulcer according to size, depth, shape, and location. A proper assessment helps in mapping the progression of ulcer during treatment. Proper assessment also necessary to figure out the type of ulcer-whether it is neuropathic, ischemic, or neuro-ischemic. The 10g monofilament is an objective and simple instrument used in screening the diabetic foot for loss of protective sensation. The device is placed perpendicular to the skin, with pressure applied until the monofilament buckles. If a patient fails to sense the pressure of a 10-g monofilament, it proves the presence of peripheral sensory neuropathy (Han et al., 2021). The general signs and symptoms of infection are swelling, warmth, tenderness, pain, erythema, and purulent secretions. But peripheral neuropathy patients can not feel the pain and patients with peripheral vascular disease may not have erythema, warmth, or swelling (Bergman & Shah, 2016). In such cases secondary signs of infection (abnormal coloration around the wound, a fetid odor from the infected ulcer, friable granulation tissue, and undermining of the wound edges) need to be assessed.

The classification of ulcerations not only helps in the prediction of prognosis but also ensures a more rational approach to therapy. Though several wound classification systems are available, but the Wagner ulcer classification system is most widely accepted. The only limitation of this method is not capable of addressing two essential parameters: ischemia and infection (Robert, 2002)

Wagner Ulcer Classification System

- Grade 0 - No open lesions; may have deformity or cellulitis
- Grade 1 - Superficial diabetic ulcer
- Grade 2 - Ulcer extension to ligament, tendon, joint capsule, or deep fascia without abscess or osteomyelitis
- Grade 3 - Deep ulcer with abscess, osteomyelitis, or joint sepsis
- Grade 4 - Gangrene localized to portion of forefoot or heel
- Grade 5 - Extensive gangrenous involvement of the entire foot

4.2. Treatment

Effective management of diabetic foot infection requires appropriate antibiotic therapy, surgical drainage, debridement and resection of dead tissue, appropriate wound care, and correction of metabolic abnormalities.

4.2.1. Antibiotic therapy

Systemic antibiotic therapy is always necessary for the treatment of clinically infected wounds but is often insufficient to cure moderate to severe DFIs. Choice of empirical and distinct antibiotic agent, route of administration, and duration of treatment are the factors need to be considered while choosing antibiotic therapy (Bader, 2008). The severity of the infection, history of recent antibiotic treatment, previous infection with resistant organisms, recent culture results, current Gram stain findings, and patient considerations should all be considered when prescribing antibiotics (Bader, 2008). Broad-spectrum antibiotics are usually given first in routine care. Hospitalization and intravenous (IV) antibiotic therapy may be necessary in severe cases where significant osteomyelitis is suspected (Ramirez-Acuña et al., 2019). Oral antibiotic therapy covers activities against Gram-positive Staphylococci and Streptococci.

The most used broad-spectrum agents are carbapenems β-lactam, or β-lactamase inhibitor combinations, such as piperacillin/tazobactam, ampicillin/sulbactam, and ticarcillin/clavulanic acid. Anaerobic bacteria are preferred to be treated with metronidazole, which is also used for the management of chronic DFU infection (Aggarwal et al., 2012). Current guidelines suggest cefoperazone/sulbactam or piperacillin/tazobactam with clindamycin are practical choices of antibiotics for DFIs (Ramirez-Acuña et al., 2019). For the treatment of chronic deep bone infection, antimicrobial therapy with surgical treatment or debridement is essential. On the other hand, in hospital settings, Methicillin-resistant Staphylococcus aureus (MRSA) is a major disease that frequently affects individuals with DFUs. MRSA infection is caused by a type of Staphylococcus bacteria that's become resistant to many of the antibiotics. If there is a high incidence of MRSA in the infection site, empiric therapy (It refers to antibiotics that are administered during the period prior to the receipt of blood culture and antibiotic susceptibility test results) against MRSA is considered (Ramirez-Acuña et al., 2019). Although a 50 percent increase in reports of resistance to vancomycin has led to the usage of linezolid, it is still the most extensively used medication in MRSA treatment (Ramirez-Acuña et al., 2019).

4.2.2. Debridement

Debridement is the removal of damaged tissue or foreign objects from a wound. It promotes granulation tissue production and can be achieved surgically, enzymatically, biologically, or through autolysis (Alexiadou & Doupis, 2012). Debridement can be done in various ways: Surgical, enzymatic, biological and autolytic. Surgical debridement is a rapid and effective way to remove hyperkeratosis and dead tissue. A scalpel blade with the tip pointed at a 45˚ angle is used to remove all nonviable tissue so that a healthy bleeding ulcer bed is can be produced with saucerization of the wound edges (Alexiadou & Doupis, 2012). For enzymatic debridement some agents like: crab-derived collagenase, collagen from krill, papain, a combination of streptokinase and streptodornase, dextran etc. are used (Alexiadou & Doupis, 2012). Enzymatic debridement can be a good option as surgical debridement is extremely painful in some cases. Biological debridement can be achieved by using sterile maggots as maggots have the ability to digest surface debris, bacteria, and necrotic tissues, leaving healthy tissue intact (Alexiadou & Doupis,

2012). Lastly, autolytic debridement means the use of dressings (hydrocolloids, hydrogels, and films) that create a moist wound environment allowing host defense mechanisms (neutrophils, macrophages) to clear devitalized tissue using the body's enzymes. Among all of these surgical debridement is the one of the gold standards in wound healing management (Alexiadou & Doupis, 2012).

4.2.3. Surgical methods

Surgery is the cornerstone of treatment for deep diabetic foot infections that may reduce the need for amputation in severe cases (Tan et al., 1996). In DFIs, the primary goals of surgery are to remove necrotic tissue, evacuate pus, and decrease the risk of further spread (Uçkay et al., 2015). Severe infections in an ischemic limb, necrotizing fasciitis, gas gangrene, and infections associated with compartment syndrome all require immediate surgery. In patients with osteomyelitis (Bone infection caused by bacteria or fungi) surgical excision of the affected bone has traditionally been the standard of care. The wound could also be treated surgically with a flap or graft, or it could be managed with negative pressure dressings (Pittet et al., 1999). A two-stage amputation (initial guillotine with later revision) may result in better primary stump (The distal end of a limb left after amputation) healing for individuals with wet gangrene or sepsis than a one-stage operation (Uçkay et al., 2015)

4.2.4. Other techniques

a) Negative pressure wound therapy

Negative pressure wound therapy (NPWT) is a method of drawing out fluid and from a wound to help it heal. This therapy was introduced 20 years ago and now is used for wound healing. According to a systematic review, NPWT treated wounds healed more rapidly than conventional dressing receiver (Uçkay et al., 2015). There are many studies regarding NPWT but none of them are that much strong. That’s why more trials are needed to better understand what role this instillation technique may have in treating DFI.

b) Wound Off-Loading

Offloading refers to the minimisation or removing weight placed on the foot. It helps to heal and prevent ulcers, particularly those caused by poor circulation to the feet due to diabetes. Offloading can be done by using a wheelchair or crutches, or through more practical means for the patient such as total contact casts (TCC) or removable cast walkers. The idea is to protect the wound from getting worse or becoming infected because of added weight on the area. Off - loading leads to ulcer healing in 90% cases within short time but there is a lack of sufficient evidence for this (Uçkay et al., 2015).

c) Wound Dressing

Wound dressings keep the wound moist, which aids in the absorption of exudate, the prevention of infections, and the healing of ulcers. There are a variety of dressing types available like- alginates, foam dressing, hydrocolloids, hydrogels, iodine preparations, low-adherence, silver-impregnated etc. (Lim et al., 2017). According to a number of studies, bioactive dressings containing insulin and fibroblasts show promising potential in the treatment of DFUs, promoting neovascularization, collagen deposition, and wound healing (Perez-Favila et al., 2019). There is no evidence that hydrocolloid or foam dressings are more effective than normal dressings.

d) Adjunctive Treatments

Adjunctive Treatment refers to a therapy that is given in addition to the primary or initial therapy to maximize its effectiveness. Hyperbaric oxygen therapy, wound stimulating factors, stem cell therapy, acellular bioproducts, human growth factors, skin grafts and bioengineered skin, energy-based therapies etc. are useful methods to heal the ulcer and to reduce rate of amputation. (Uçkay et al., 2015). As these techniques are new that's why more experiments, trials and investigations need to be done so that they can be used properly.

4.3. Emerging treatments

Increased antibiotic resistance has stimulated research into non-antibiotic treatments for various types of DFI. Treatment options like- photodynamic inactivation, bactericidal laser therapy, and phage therapy etc. are showing good results (Uçkay et al., 2015). Some drugs like ciprofloxacin-loaded calcium alginate wafer, WF10, PFD, DFO, Nitroglycerine etc. showed positive result in terms of treating DFU (Ramirez-Acuña et al., 2019). A photographic foot imaging device have been developed so that home monitoring can be done for early diagnosis. (Uçkay et al., 2015). Infrared thermometry, infrared thermal cameras etc. are kind of devices that help to measure the complications. A quantum dot-based foot mapping system help to visualize infection.

Table: Some other available treatments for DFU

Treatment Techniques	Details	References
1. Larval (maggot) Therapy	In this method, maggots are sterilized and placed directly on wounds for treating infection. *Lucilia cuprina* (blow fly) is the mostly used maggots for DFU treatment.	(Perez-Favila et al., 2019)
2. Antimicrobial Peptides (AMPs)	AMPs are molecules of the immune system of mammals whose function is to fight the invading pathogens. They are used with conventional antibiotics for treating infection. Some AMPs are: nisin, helical antimicrobial decapeptide KKVVFWVKFK (KSL-W), ubiquicidin 29-41 (UBI 29-41), pexiganan (MSI-78), and beta-defensin-2 (hBD2)	(Perez-Favila et al., 2019)
3. Revascularization	Revascularization helps to improve blood flow in ischemic foot which is beneficial for treating infection.	(Lipsky, 2004)
4. Hyperbaric Oxygen (HBOT)	This technique is administrated in a compression chamber, which provides 100% oxygen and delivers a greatly increased partial pressure of oxygen to tissues. This oxygen helps to fight infection and improves wound healing.	(Everett & Mathioudakis, 2018)

5. Laser therapy	In Low-level laser therapy (LLLT), light is used in the form of light emitting diodes. LLLT can reduce the inflammatory phase, favoring the angiogenesis and the production of extracellular matrix components, which increases the healing process.	(Perez-Favila et al., 2019)
6. Growth Factors	Growth factors are proteins that can stimulate and activate angiogenesis, transcription of genes, and other reactions that increase wound healing. Epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), platelet-rich plasma (PRP) – are the most common ones.	(Perez-Favila et al., 2019)
7. Scaffolds	Two types of Matrices are used for wound repair: natural and synthetic. The natural matrices are collagen, hyaluronic acid, fibrin, chitosan, and alginate. Poly (acrylic acid), polyglycolic acid, poly (lactic-co-glycolic acid), poly(e-caprolactone), PCL-poly (ethylene glycol), gelatin methacrylate, and pluronic F-127- are the synthetic ones.	(Perez-Favila et al., 2019)

8. Skin grafts and bioengineered skin	Skin grafting adds extracellular matrices which induce helpful growth factors and cytokines. Recent studies have showed that allografts originating from dehydrated human amniotic and chorionic membranes (dHACM) improve the rates of wound healing compared to standard care.	(Everett & Mathioudakis, 2018)
9. Phototherapy	Phototherapy generates photochemical reactions that increase cellular metabolic activity and cell proliferation, vasodilation, and angiogenesis, all of which can speed wound healing. Phototherapy can also be useful for reducing ulcer size.	(Everett & Mathioudakis, 2018)
10. Acellular bio products	Acellular dermal matrix (ADM) plays important role in wound healing by providing structural support and signals to modulate cellular responses. It provides a barrier to bacteria and a moist wound environment, which increases cell regeneration. Use of DermACELL (ADM) and Graftjacket ADM showed effectiveness in ulcer healing compared to conventional treatment.	(Everett & Mathioudakis, 2018)

11. Systemic therapies	Several systemic agents like low-molecular-weight heparin, iloprost infusion, vildagliptin, oral pentoxyyfilline, and many herbs are used to treat ulcer. Several studies found that various vitamins and supplements (magnesium, omega-3 fatty acids, zinc sulfate, and vitamin D) can increase wound healing process.	(Everett & Mathioudakis, 2018)

4.4. Lifestyle Management

The cornerstone of treatment of patients with diabetes is lifestyle management. In fact, with proper management, a diagnosis could lead to a longer and healthier life. As diabetes creates other various complications in the body so taking necessary steps to maintain a healthy life is important. The preventive measures and management of diabetic complications consists of lifestyle modification, blood pressure control, lipid management, glycemic control, smoking cessation etc. (Bergman & Shah, 2016). Taking healthy food (low in sugar, fat, carbohydrate) will help to maintain the blood sugar and lipid; only 30 minutes of physical activity will eliminate bad toxins from body and will lower the blood sugar along with the risk of heart disease. Regular checkup is necessary to detect if there is any complication, infection, nerve damage or not. If the health of a diabetic patient is good, then other diabetic related complications will not affect. Though diabetes related foot disease is very common in diabetic patients but practicing some lifestyle changes may prevent or reduce the risk of amputation. The hand and feet need to keep clean and dry. Patients must wear properly fitted shoes to avoid any accident. The socks also need to be washed regularly, tight socks and shoes should be avoided. Patients with diabetic neuropathy must use proper footwear both indoors (Iraj et al., 2013). Some little lifestyle changes like these, will make a big difference in patient's health.

Chapter 5 : Prevention

Diabetic foot ulcers can be preventable. Proper training to patients plays an important role in prevention of DFU. The ultimate object of training is to motivate the patient and develop skills to maximize the use of preventive measures. It is also required to ensure that the patients have understood all the instructions.

5.1. Glycemic Control

Blood glucose control is commonly suggested to enhance wound healing and avoid negative effects on cellular immunity and infection. A study stated that those with intensive glycemic control had a 35% reduction in risk of lower-extremity amputation (Everett & Mathioudakis, 2018). Regular exercise, maintained carb intake, eating fiber containing food, drinking enough water, routine checking of blood glucose level etc. are the effective ways for glycemic control.

5.2. Blood Pressure Control

The importance of effective blood pressure control in type 2 diabetic patients to prevent cardiovascular outcomes and other diabetes-related complications. Patients with diabetes should achieve a target blood pressure of less than 130/80 mm Hg. According to CDC, healthy lifestyle habits can help to prevent high blood pressure. Like- regular exercise, healthy diet, limiting alcohol and salt intake, quitting smoking, losing extra weight etc.

5.3. Lipid Management

Accumulation of specific lipid metabolites contributes to lipid-induced hepatic insulin resistance. Increased intracellular lipids also leads to hyperglycemia, as well as diabetic dyslipidemia associated with increased cardiovascular disease (CVD) risk. Weight loss, increased physical activity, reduced saturated/trans-fat and cholesterol consumption, as well as increased intake of omega-3 fatty acids, viscous fiber, and plant stanols/sterols, are all important factors in improving the lipid profile in diabetics.

5.4. Smoking Cessation

Managing diabetes is challenging, and smoking can make it even more so. Nicotine increases blood sugar levels and makes them harder to handle. Chemicals present cigarettes can slow down healing process which may prevent a full recovery from a foot ulcer. Quitting smoking helps the body to use insulin better, which can make the blood sugar levels easier to manage. Some practices for example- trying nicotine replacement therapy, avoiding triggers, chewing on sugarless gum or hard candy, doing physical activity, practicing relaxation techniques can really help.

5.5. Nail and Skin Care

According to the recommendation of American Diabetes Association, diabetic patients need to inspect, wash, and gentle cleansing with soap and water, followed by application of topical moisturizers, aids in the maintenance of healthy skin that is more resistant to breakdown and injury. An annual comprehensive foot examination by a health care provider is necessary. Any kind of small cut, injury or infection can be treated by home remedies but hot soaks, heating pads, and topical agents such as hydrogen peroxide, iodine, and astringents should be avoided. Minor wound cleansing and the use of a topical antibiotic to keep the wound moist can help to prevent the formation of ulcers.

5.6. Proper Foot ware

To prevent diabetes related foot disease, it is recommended to wear proper footwear and keep the feet clean and dry. Walking barefoot is not recommended, so diabetic patients should always wear shoes and socks. If the patient has a history of foot problems, more frequent examinations are advised. Custom shoes may be beneficial for patients with foot deformities or special support (David et al., 1998). People who are at low risk of developing a diabetic foot problem should continue to have annual foot assessments. The people who are at moderate or high risk should be referred to the foot protection service for advice on how to keep their feet in good condition (David et al., 1998).

Chapter 6: Discussion

According to International Diabetes Federation, approximately 537 million adults (20-79 years) are living with diabetes. People with diabetes have an increased risk of developing several serious health problems. Constant high blood glucose level affects the heart and blood vessels, eyes, kidneys, nerves, and teeth. In addition, patients also have a higher risk of developing infections.

Diabetic foot infection is the most common, complicated, and expensive complication associated with diabetes, found in 6.3 percent of the world's population (Zhang et al., 2017). About 15–25% of patients with diabetes may develop foot ulcer during their lifetime (Yazdanpanah et al., 2018a). Peripheral arterial disease (PAD), diabetic Neuropathy, poor sugar control, chronic ulceration, prior lower extremity amputation & lifestyle are the main risk factors for diabetes related complications. Among all of these, Peripheral arterial disease (PAD), Diabetic Neuropathy contribute the most. According to a number of studies, PAD is an independent risk factor and present in 50% of patients with diabetic foot ulceration (Brownrigg et al., 2013). On the other hand, Diabetic neuropathy is a factor in almost 90% of diabetic foot ulcers (Boyko et al., 2015).

DFU is a significant cause of morbidity and can result in lengthy hospitalization. It is responsible for 20% of diabetes-related hospitalizations (Madanchi et al., 2013). DFU patients have a high death rate, almost twice that of individuals without ulcers (Banik et al., 2020). Standard practices in DFU management include proper assessment, antibiotic therapy, surgical debridement, dressings, wound off-loading, vascular assessment, infection control, glycemic control etc.

Patients with DFU should immediately start treatment once the ulcer is noticed. Proper treatment not only reduce the risk of infection and amputation but also improve quality of life and health care costs. Among the available treatments, antibiotic therapy and surgical debridement are the most common and effective way of treating infections but now-a- days research is going on to use other techniques effectively. Along with the treatments, developing a healthy lifestyle is must to prevent and control diabetic related foot diseases. Lifestyle modification, blood pressure control, lipid management, glycemic control, smoking cessation etc. (Bergman & Shah, 2016) would help to maintain a good health and lower the risk of other life-threatening disease (Bergman & Shah, 2016).

Diabetic foot ulcers can be preventable. To prevent its development in the first place is the best way to treat a diabetic foot ulcer. Doctors recommend diabetic patients should receive adequate training to know how to inspect their feet regularly and should know how to recognize a problem with their feet before it becomes a major issue. Learning how to check feet properly is very crucial. Patients need to inspect their feet everyday-specifically between the toes and the sole for cuts, cracks, bruises, blisters, redness, ulcer, or any sign of abnormality. Daily cleaning, proper footwear, managing blood sugar levels, maintaining a healthy weight, quitting smoking and alcohol can help to remain healthy, which not only speed up the healing but also prevent the ulceration.

Chapter 7: Conclusion

Diabetic foot ulcer (DFU) is the most common and neglected complications of diabetes. Diabetic foot issues contribute to both mortality and morbidity in the diabetic population, putting individuals and the community at large under significant physical, emotional, physiological, and financial strain. The main risk factors include age, gender, peripheral arterial disease (PAD), diabetic neuropathy, poor sugar control, chronic ulceration & poor lifestyle.

Management of DFU is a multidisciplinary approach started with proper assessment and detection. Early detection and treatment can help to prevent infection and keep the sore from getting worse. Antibiotic therapy and surgical debridement are the most effective ways of treating DFU. Along with other treatment, lifestyle modification plays a great role in management.

Prevention of diabetic foot ulcer is the key to reduce the associated high rates morbidity and mortality along with the danger of limb amputation. It is necessary to identify the “foot at risk” by means of physical examination followed by neuropathy and vascular tests. Patient education, simple hygienic practices, prompt treatment of minor injuries significantly reduce the ulceration. All the patients need to use proper foot ware both indoor and outdoor to avoid any accidental cut and infection. Patients with diabetes should have proper knowledge so that DFU can be prevented and managed more effectively.

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